NATIONAL CANCER INSTITUTE

GENERAL STATEMENT

The National Cancer Institute (NCI), established under the National Cancer Act of 1937, is the Federal Government's principal agency for cancer research and control. The National Cancer Act of 1971 directed the Institute to coordinate the National Cancer Program encompassing programs of the NCI and cancer research in other NIH Institutes and other Federal and non-Federal programs.

Laboratory and clinical investigations relating to the cause, prevention, diagnosis, and treatment of cancer as well as research in cancer control related to cause and prevention, detection and diagnosis, therapy and rehabilitation, and education and training should be assigned to the NCI when related to:

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NCI GENERAL STATEMENT (CONT.)

SPECIFIC AREAS OF INTEREST

I. IMMUNOLOGY

The Immunology Program supports research that contributes to an understanding of the role of the immune system in controlling the development, growth, and spread of tumors, and includes studies of basic transplantation biology relevant to tumor rejection and to immune reconstitution. Also included is the development of technologies to facilitate this research. The specific areas of investigation include:

- Synthesis, structure, and function of antibodies capable of reacting with tumor cells, agents that induce tumors, agents used in the treatment of tumors, and agents used to modulate the immune response to tumors; antibodies produced by tumors, e.g., myeloma proteins

- Synthesis, structure, and function of soluble factors that participate in, activate and/or regulate hematopoietic cell growth and the immune response to tumors, including the interferons, other lymphokines and cytokines (interleukins), hematopoietic growth factors (T cell growth factors, B cell growth factors, colony stimulating factors, etc.), helper factors, suppressor factor, and cytotoxic factors

- Immunobiology of lymphocytes, macrophages and other cells that are capable of participating in the immune response to tumors, including hematopoiesis, differentiation, heterogeneity, interactions, and especially, functions. These cell types include T-cells, B-cells, macrophages, natural killer cells, lymphokine-activated killer cells, neutrophils, etc.

- Identification, immunogenetics, isolation, and characterization of cell surface molecules of lymphocytes, macrophages, and other cells that are involved in the responses of these cells to tumors.

  This includes studies of genetic regulation of their expression and function. These molecules include specific receptors (e.g., T-cell receptor), restriction elements (major histocompatibility complex class I and II antigens), adhesion molecules, and accessory activation molecules

- Intracellular events activated by functional interaction of tumor cells with a component of the immune system. These events, which may occur in either the tumor cell or a cell of the immune system, include ion fluxes, protein phosphorylation, and other mechanisms leading to functionally relevant gene activation or repression

- Identification, isolation, and characterization of cell surface molecules on tumor cells which serve as target antigen for the immune response, e.g., tumor-associated antigens, and the genes that regulate their expression

- Mechanisms that regulate hematopoiesis, in particular, biological studies of the differentiation programs of immune cells and malignant hematopoietic cells

- Biology of hematologic malignancies, i.e., leukemias and lymphomas (including AIDS-associated lymphomas), addressing subjects such as biochemical, and immunologic markers for the classification and characterization of neoplastic cells and their normal counterparts

- Studies on immunopathology of the host-tumor interaction

- Immune status of tumor-bearing animals and man, including studies on immunostimulation, immunosuppression, and the effects of disease on immune function

- Basic studies on the role of immunodeficiencies (including AIDS) in the development of malignancies; animal models of AIDS-associated malignancies; immunopathology of AIDS-associated malignancies

- Immunotherapy in animal models and man, where the main emphasis is upon the study of immune parameters, immune mechanisms, and other immunologic concerns rather than upon a therapeutic result; specific and nonspecific stimulation of the immune system using natural and synthetic agents

- Development of strategies and study of mechanisms relevant to vaccine approaches to the treatment and/or prevention of cancers of non-viral etiology

- Bone marrow transplantation in man and animals with cancer, when the emphasis is on immunologic problems, such as immune reconstitution (stem cell growth, engraftment), sensitization (graft rejection), graft versus host disease, and graft versus leukemia effects

- Technology development to facilitate studies relating to basic cancer immunology

II. CANCER BIOLOGY

Biological differences between normal and cancer cells. These studies use mechanistic approaches to explore tumor cell biology and tumor progression at the molecular and cellular level and to examine cell-cell and cell-matrix interactions at the macro-molecular level in whole tissues. Models utilized in these studies may be tumor tissues or tumor cells, their components, or their products. Also included is the study of the pathology and biology of solid tumors and tumor-bearing animals, and chimeric, transgenic and knock-out animals. Additionally, research focused on the development of technologies to facilitate these studies

- Molecular Biology
  functional analysis of oncogenes and suppressor genes and their products, including their involvement in the regulation of gene expression

  functional consequences of post-transcriptional processes such as splicing, polyadenylation, mRNA transport and stability, and protein translation

  function consequences of genomic imprinting

  basis for genetic instability as it relates to the cell cycle

- Biochemistry
  biosynthesis and modification of glycoproteins and proteoglycans

  regulation of DNA replication

  identification of functional domains of onco-proteins and tumor suppressor proteins and cellular proteins with which they interact

  characterization of protein modifications, e.g. phosphorylation, glycosylation, methylation, prenylation, and isolation and functional analysis of the enzymes responsible for the modifications

  characterization of mitochondrial enzymes and energy metabolism

  functional and biochemical characterization of the components of all signal transduction

pathways, identification and analysis of factors that regulate the cell division cycle, e.g. cyclins, cyclin-dependent kinases, cyclin inhibitors and cell cycle check points

dysregulation of intracellular protein localization

- Cell Biology
  biosynthesis and function of cellular and nuclear membranes
  regulation during cell division

  basic mechanisms of endocytosis and exocytosis

  molecular characterization of cell-cell interaction and communication through gap-junctional structures, connexins and cadherins

  elucidation of the role of the cytoskeleton in cell division, shape, migration, transport, and signal transmission

  characterization of nuclear matrix, its components and its properties

  extracellular matrix and basement membrane composition, structure, synthesis, and biology of collagens, fibronectins, laminin, proteoglycans and tenascin

  interactions among matrix components

  isolation and characterization of enzymes such as proteases, enzyme inhibitors and other factors that influence the matrix

  molecular basis of adhesion and motility and involvement in migration and invasion

  role of stromal components in cell signalling, growth and differentiation

  cell adhesion molecules (CAMs) including integrin receptors and selectins, their properties and role in signal transduction, growth and differentiation

  growth factors, protein and peptide hormones and their receptors

  purification and characterization of growth inducers and inhibitors

  identification and characterization of receptors

mechanism of action of paracrine and autocrine factors

identification of stem cells susceptible to transformation

cell products that influence bone turnover

characterization of the process of apoptosis, including identification of inducers and inhibitors, their associated signal transduction pathways, and their interaction with the cell cycle

- Endocrinology
  - mechanisms of growth induction by hormone-receptor interaction, including steroids, retinoids and vitamin D
  - identification and cloning of unique tumor cell steroid receptors
  - mechanisms of hormone independence
  - influence of growth factors on endocrine responses
  - mechanisms of growth regulation by steroid hormone antagonists
- Angiogenesis
  - inducers and inhibitors of neovascularization including growth factors
  - regulation of endothelial cell biology and growth
  - identification and evaluation of secreted cell factors related to angiogenesis regulation
- Metastasis
  - processes and enzymes involved in cell adhesion, migration, invasion, extravasation, and hematogenous and lymphatic dissemination of cells
  - identifying gene products responsible for metastatic capability
  - identification of factors that influence colonization
  - process of tumor progression
  - development of appropriate new animal and cellular models for metastasis

ECM degradation and remodeling

tumor-stromal interactions

- Nutrition
  identification of requirements for neoplastic growth

  analysis of the role of dietary metabolites in tumor progression

  regulation of calcium metabolism

  nutrient-hormone interaction

- Technology development to facilitate studies relating to basic cancer biology research

III. CANCER GENETICS

Basic research, at the cellular and molecular levels and in model systems, on genes that, when altered, lead to malignant transformation and tumor progression. Research focuses on gene structure, function and regulation of expression, and could include studies of chromosomal abnormalities, chromosome structure (including DNA methylation, fragile sites, and recombination events), identification of novel oncogenes or tumor suppressor genes, regulation of gene expression (alterations of transcription or gene products), DNA repair mechanisms, the effects of alterations in genes and their expression on tumor development, and the development of technologies to facilitate this basic research.

- Cancer Genetics and Molecular Genetics
  identification, isolation, cloning, and functional analysis of genes causally involved in malignancies

  characterization of the genes involved in tumorigenesis, including verification of candidate cancer gene status, studies of genomic structure, identification of major regulatory regions and mechanisms, and identification of dysregulation mechanisms

  identification and analysis of chromosome aberrations at the gene level, including genes involved in translocations, deletions, inversions, and amplifications

  regulation of the expression of cancer genes by identification and characterization of transcriptional elements (promoter, enhancer, silencer, etc.) and the proteins that bind to

those elements and by characterization of the initiation, elongation, and termination cesses

characterization of post-transcriptional cancer gene expression regulatory processes, such as polyadenylation, splicing, mRNA transport, editing, stability, turnover, and translation

- Chromosome Structure and Mechanisms
  identification and characterization of cancer chromosome aberrations at the structural level, including translocations, deletions, inversions, amplifications, fragile sites, and repeat expansions

  identification of the molecular basis (inherited genes, LOH, aberrant DNA replication, recombination, repair) for genetic instability

  identification of the chromosome structural and functional features that regulate cancer gene activity (locus control regions, imprinting or DNA methylation, position effects, nuclear matrix attachment, histone modifications, etc.)

  composition, function, and biochemical modification of chromatin and nuclear matrix

- Genetic Models of Malignancy (cellular, eukaryotic, vertebrate, mammalian)

  for identifying the molecular basis for inherited malignancies and those mechanisms (modifier loci, quantitative trait loci, compensatory mutations, etc.) that alter the penetrance of cancer-predisposing genes

  for complementation of cancer genes to aid in their identification, functional assignment, and definition of gene networks

- Structure studies (by X-ray crystallography, diffraction spectroscopy, NMR, etc.) of cancer gene products and their interactions with nucleic acids

- Technology development to apply genomic approaches to basic cancer genetics and biology research

IV. BIOLOGICAL CARCINOGENESIS

Biological carcinogenesis research concerns studies of the role of biological agents as factors or cofactors in the etiology of human and animal cancer. The biological agents of primary interest are viruses, although the research program may encompass all forms of life,

including bacteria and other microbial agents. Studies encompass a wide range of approaches, including basic biochemistry and molecular biology of oncogenic and suspected oncogenic agents, viral oncogenes and associated tumor suppressor genes, pathogenesis and natural history studies, animal models, and preventive vaccine research. Also included is the development of technologies to facilitate studies relating to biological carcinogenesis research.

- o Study of basic mechanism(s) of causation of human and animal cancers by biological agents, primarily viral but also including bacterial or fungal agents and any other form of life.

- o Isolation, identification, characterization, and biological activity of oncogenic and/or suspected oncogenic and biological entities, such as viruses, viral oncogenes, viral gene products, and bacteria; elucidation of their role in cell transformation and induction of neoplasia

- o Basic and fundamental studies leading to the development of vaccines for human cancers of viral or bacterial etiology, including but not limited to papillomavirus associated with cervical and anogenital carcinoma, Epstein-Barr Virus (EBV) associated with nasopharyngeal carcinoma, Burkitt's lymphoma and other malignancies, hepatitis viruses associated with liver cancer, Helicobacter pylori associated with gastric cancer, HTLV associated with adult T-cell leukemia and lymphoma, and Kaposi's sarcoma-associated viruses

- o Interaction of oncogenic viruses, bacteria, or microbial genes with environmental factors, hormones and/or host tissues, including proto-oncogenes and tumor suppressor genes (anti-oncogenes), and proteins in the induction of human and animal cancer

- o Etiologic role of viral oncogenes, in combination with or in antagonism to cellular suppressor genes, and proto-oncogenes in human and animal cancer

- o Basic, laboratory and animal model studies of human oncogenic retroviruses such as human T-cell lymphotropic virus type I (HTLV-I) and HTLV-II and their non-human animal host counterparts, the bovine leukemia virus (BLV), simian T-cell lymphotropic virus (STLV), and simian retroviruses (SRV)

- o Basic, laboratory, and animal model studies relating to DNA tumor viruses, such as EBV, papillomaviruses, papovaviruses, Kaposi's sarcoma-associated viruses, etc.

- o Basic and fundamental studies of mutations in viruses and viral oncogenes providing clues to cancer therapy

- Development of viral vectors such as herpesvirus, adenovirus, and retrovirus for gene therapy of cancer

- Biological and biochemical studies on emergent viruses or bacteria of concern in human cancers, e.g., retroviruses, HTLVs, HIV, hepatitis C virus, papillomaviruses, HHV6, HHV8 (KSHV) and H. pylori

- Effects of oncogenic viruses or bacteria on cellular structure and function, including, but not limited to, studies of viral induced/associated tumor antigens

- Viral or bacterial mediation of cellular apoptosis

- Interaction of viral genes with host cell components leading to mutation, chromosomal translocation, and development of cancers, such as Burkitt's lymphoma, chronic myelogenous leukemia, non-Hodgkin's lymphoma, gastric cancer, hepatocellular carcinoma, papilloma virus associated cervical neoplasia, adult T-cell lymphoma, Hodgkins disease, Kaposi's sarcoma, pleural effusion lymphomas, Castleman's disease

- Animal model systems such as transgenic animals, knockouts and others in studies of viral or bacterially induced or associated human and animal cancer

- Integration, expression, and intracellular control of oncogenic or suspected oncogenic viruses or bacteria, including replication, transcriptional and translational regulation

- Characterization of molecular and biological interactions linking long-term carriage of certain infectious viruses or bacteria, e.g., hepatitis B virus, hepatitis C, EBV, SV40, HSV, HHV8(KSHV), cytomegalovirus (CMV), papillomaviruses, retroviruses, HTLV-1, HTLV-2, HIV with human and animal malignancy

- Role of viral-associated growth factors in the induction of human and animal cancers

- Relationship between oncogenic or suspected oncogenic viruses or bacteria and host cell surface membranes/ receptors/structures/organization

- Relationship between cancer virus infection/ replication/transformation/viral latency and cell permissiveness/non-permissivenesss.

- Kinetics, mechanisms, and regulation of oncogenic virus or bacteria infection, induction of latency and persistent infection, and events of cell transformation

- Regulation of viral macromolecular synthesis, viral protein transport, virion assembly in productive and abortive infections, in permissive and non-permissive cells

- Development of methodologies for studies of oncogenic viruses or bacteria, including the use of serological procedures and retroviral vectors and test methods with diagnostic/prognostic value for virally induced human and animal cancer

- Studies leading to eventual control of oncogenic virus or bacteria infections or prevention of cancer induction in humans or animal models, including research and preclinical evaluation of prophylactic or therapeutic cancer vaccines for cancers of known or suspected viral or bacterial etiology, interferon, and immunotherapy directed toward viral antigens or epitopes

- Studies of the biology of virus-host interactions or the biology of tumor bacteria; humoral and cell-mediated immune responses against oncogenic viruses, their proteins and epitopes; relationship of viral tumorigenesis to host immune function

- Studies of cancer viruses or bacteria in hyperplastic and non-neoplastic disease states

- Basic and fundamental laboratory studies leading to the development of an AIDS vaccine, including, but not limited to: identification of gene products of pathognomonic significance, identification of protective epitopes, studies on the nature and time course of the host response to individual virus antigens, studies on antigen delivery, studies in vitro and in vivo to determine the nature of a protective host response, and initial evaluation in appropriate animals.

- Malignant sequelae of AIDS (such as Kaposi's sarcoma, Castleman's disease, pleural effusion lymphomas, leiomyosarcomas and B-cell non-Hodgkins lymphomas); the role of viruses, viral proteins, growth factors, and cytokines in the etiology of viral associated AIDS malignancies; animal models of AIDS associated malignancies; pathogenesis of AIDS associated malignancies

- HIV genetic variants and their etiologic role in the development of neoplastic sequelae of AIDS

- Development of technologies to promote studies concerned with the role of biological agents as factors or cofactors in the etiology of cancer

V. CHEMICAL AND PHYSICAL CARCINOGENESIS

- Isolation, molecular structure, synthesis and characterization of known and suspect chemical carcinogens and their metabolites; evaluation of molecular structure-activity relationships

- Characterization of carcinogen-macromolecular interactions, i.e., site specificity, conformational analyses; changes in macromolecules and other cellular components; alterations in cell functions produced by genotoxic and nongenotoxic chemical carcinogens and co-carcinogens

- Carcinogen-induced cell transformation, including genetics (oncogenes and tumor suppressor genes such as p53, RB, etc.) and mechanisms of induction; viral-chemical interactions in the induction of cell transformation

- Characterization of biological responses to physical carcinogens such as metals, minerals and prosthetic materials

- Identification, quantitation and mechanism of formation of biochemical and molecular markers of carcinogen exposure

- Properties of cells transformed by carcinogens, e.g., cell membrane, enzyme, and ultrastructural changes

- Regulation of carcinogen metabolism, including genetic and dietary factors; isolation and characterization of carcinogen-metabolizing enzymes

- Role of growth factors (IGF, EGF, TGF, etc.) in chemical and hormonal carcinogenesis

- Relationship of mutagenesis and genetic damage by genotoxic and nongenotoxic chemicals and metals (e.g., chromosomal aberrations, SCE, etc.) to cancer etiology

- Development of carcinogenicity testing procedures

- Metabolism, toxicity and physiological disposition of carcinogens and their metabolites; identification of reactive metabolites binding to proteins and/or other macromolecules (DNA adducts)

- Exocyclic nucleic acid derivatives in carcinogenesis resulting from reactions with carcinogens and genotoxic compounds such as acrolein, vinyl chloride, malondialdehyde, etc.

- Identification, quantitation and properties of tumor promoters such as phorbol esters and endogenous compounds; nature and mechanisms of tumor promotion (i.e., signal transduction, ODC induction, etc.)

- Role of oxygen radicals and other free radicals in carcinogenesis and tumor promotion; inhibition/ suppression of free radical carcinogenesis/promotion

- Inhibition, arrest, reversal or delay of the carcinogenesis process, including inhibition of the formation of intermediate biomarkers by chemical compounds and biological agents in experimental models and inhibition of tumor promotion/progression

- Inhibition/suppression of growth factor- and hormone-mediated carcinogenesis

- Design, synthesis and molecular characterization of potential chemopreventive agents and analogs

- Mechanisms of chemoprevention/anticarcinogenesis, including chemoprotection/chemoprevention of oncogene activation and inactivation of tumor suppressor genes

- Pharmacokinetics of chemopreventive agents

- Role of binding protein and receptor-mediated mechanisms of anticarcinogenesis/chemoprevention, including nuclear receptors of the steroid/thyroid hormone superfamily (retinoids, vitamin D and its analogs, steroid hormones)

- Isolation, purification and characterization of inhibitors/suppressors of carcinogenesis from natural sources, e.g., fruits, vegetables, fibers, plants, herbs, spices, etc.

- Role of synthetic and biological antioxidants such as vitamins A, C, E, carotenoids and amino acids and their derivatives, metabolites and analogs in chemoprevention

- Role of dietary fat, fiber, omega-3-poly-unsaturated fatty acids, macro- and micronutrients, fasting, stress and exercise in cancer etiology and prevention

- Role of phytoestrogens/xenoestrogens in carcinogenesis/anticarcinogenesis

- Role of protease inhibitors in cancer prevention

- Mechanisms of repair of DNA damage following interactions with carcinogens; characterization of defective DNA repair genetic syndromes that predispose cancer development (e.g., Bloom's syndrome, xeroderma pigmentosum, etc.); DNA repair enzymology

- Interspecies comparisons of carcinogenic response, including risk assessment extrapolation

- Development of procedures for the qualitative and quantitative analysis of body fluids and tissues for the presence of chemical carcinogens, metabolites and biomarkers of exposure

- Development of *in vitro* organ and cell culture systems and *in vivo* vertebrate and invertebrate animal models for use in carcinogenesis studies related to organ sites such as breast, prostate, pancreas, ovary, brain, etc.

- Etiology of neoplasia in poikilothermic aquatic and marine animals, amphibians, finfish and shellfish

- Role of metallothionein in carcinogenesis

- Role of peptide, protein and steroid hormones and their metabolites as factors in carcinogenesis, including their activation of oncogenes; role of hormones and metabolites in all phases of carcinogenesis, i.e., initiation, promotion and progression

- Role, fate, occurrence and metabolism of carcinogenic dietary mutagens commonly present in human foods, e.g., IQ, PhiP, IQx, MeIQx, etc.

- Tobacco carcinogenesis related to smoking, exposure to environmental tobacco smoke, and use of smokeless tobacco; determination of the metabolic fate of extractable tobacco components, whole smoke, environmental tobacco smoke, and smoke condensates

- Carcinogenesis of the oral and nasopharyngeal cavities, including interaction of diet, alcohol and tobacco use

- Tobacco specific nitrosamines NNN and NNK and studies that use these compounds in experimental tumor models

- Role of physical carcinogens such as asbestos, silica, and man-made fibers in carcinogenesis

- Technology development to facilitate studies relating to research concerned with the occurrence and inhibition of cancer caused or promoted by chemical or physical agents

VI. RADIATION EFFECTS

Biological effects resulting from exposure to non-ionizing and ionizing radiations, particularly at low doses and dose rates, from both natural and man-made sources, including the development of technologies to

facilitate this basic research. Investigations at the molecular, cellular, tissue, and whole animal levels of biological organization relate to:

- Molecular mechanisms of radiation-induced genetic damage and repair, and related effects on gene expression and regulation of cell division from exposure of mammalian and surrogate non-mammalian cells to ionizing radiation, ultraviolet (UV) radiation and other non-ionizing radiation

  Mechanisms of DNA damage and repair, mutagenesis, and large scale chromosome deletions, translocations, and rearrangements, including effects of dose and dose rate of high- and low-LET radiation, both in vitro and in vivo

  Molecular analysis of the mechanisms of delayed expression of ionizing-radiation-induced mutations

  Use of mammalian and non-mammalian model systems (e.g., chromosomal- and viral-borne target genes, repetitive DNA sequences, plasmid shuttle vectors) to analyze qualitative and quantitative effects of radiation on defined genetic sequences

  Effects of ionizing or non-ionizing radiation on gene expression, on cell differentiation, and on differentiated cells

  Effects of radiation on the immune surveillance system and its capacity to respond to radiation-induced biological effects, implicated in the etiology of cancer (e.g., cellular responses to radiation-induced DNA damage and repair)

  Effects of radiation on cell structures (e.g., membranes, endoplasmic reticulum) other than genes and gene-expression components, which may be implicated in cancer induction, promotion, or progression

  Relationship of mammalian cell cycle to radiation-induced damage and repair

  Role of tumor-suppressor genes on radiation-induced apoptosis and cell cycle arrest of eukaryotic cells, particularly mammalian cells

  Regulatory mechanisms controlling the expression of radiation-induced apoptosis in mammalian cells

- Molecular and cell biology underlying radiation carcinogenesis and teratogenesis in mammalian cells, transgenic and whole animal models:

Role of ionizing radiation from both external sources and from internally deposited radionuclides as an initiator and promoter of cancer and/or developmental defects

Comparison of cellular, tissue and organ differences in susceptibility to radiation during development and in the mature animal

Molecular basis for differences in biological effectiveness between low- and high-LET radiation

Combined effects of radiation and other carcinogenic, mutagenic and teratogenic agents

Mechanism of action and effectiveness of radiation modifiers, including sensitizers and protectors

- Identification and validation of biochemical and molecular markers for radiation exposure (e.g., mutation spectra, radiation-induced damage repair proteins, radiation-induced oncogenes, oncogene products, growth factors/receptors, cell surface proteins):

  Correlation of markers with radiation exposure as a function of dose, dose rate, and LET in both in vivo and in vitro biological systems

  Determination of temporal and spatial relationships of marker expression with premalignant progression and frank malignancy in cells, tissues and organs

- Mathematical modeling of epidemiological, animal, cellular, and molecular data to quantitate risks from low-level exposure to radiation

- Clarification of dose-effect relationships resulting from exposure to low doses and dose rates of ionizing radiation

- Technology development to facilitate studies relating to ionizing and non-ionizing radiation-induced carcinogenesis and dose assessment

VII. DIAGNOSTICS RESEARCH

- Applications of classical and molecular genetic techniques to the diagnosis, prognosis, and monitoring of cancer. Studies relating gene expression to diagnosis and prognosis

- Identification of genetic components unique to cancerous or precancerous cells, including cytogenetic and molecular genetic abnormalities (mutations,

additions, deletions, or translocations), and studies to determine their relationship to diagnosis, prognosis or monitoring

- o Genetic or physical mapping studies when the focus is on a specific gene or chromosomal region for the purpose of diagnosing cancer and predicting outcomes, including response to therapy
- o Genetic mapping studies to develop assays that may be used for assessing an individual's predisposition to cancer
- o Identification of cellular and molecular components or metabolic products unique to cancerous or pre-cancerous cells (including hormones and hormone receptors, peptides, proteins, glycoproteins, enzymes, and oncogene products) and studies to determine their relationship to diagnosis, prognosis, response to therapy and monitoring
- o Development of biological, genetic, histochemical, immunologic, and microscopic techniques to improve classification of human tumors
- o Development of techniques to detect the presence and identify the origin of metastatic lesions. Studies to identify markers of metastasic potential
- o Development of methods to measure cell proliferation and studies relating cell proliferation to cancer prognosis and response to therapy
- o Research to develop methods for early detection of recurrent neoplastic growth
- o Development of immunodiagnostic techniques for detection of tumor specific antigens
- o Studies to validate clinical applications of new diagnostic tools

VIII. RESOURCES DEVELOPMENT

- o Development and maintenance of specialized specimen resources to facilitate basic and diagnostic cancer research, including tissue banks, tissue procurement networks, and DNA banks
- o Development of new tissue processing techniques and new reagents to better preserve critical molecular components to facilitate cancer diagnostic research (for example: embedding, fixation and storage techniques)

- Informatics in support of tissue resources and diagnostic cancer research. (Such as: computer programs to access and manage clinical information, programs to manage tissue collection, storage and distribution, methods to protect the privacy of computerized clinical data, and systems for data entry and storage to standardize or reconcile clinical and pathologic terminology)

IX. TECHNOLOGY DEVELOPMENT

- Development of high-throughput, automated or semi-automated, technologies for the detection of molecular alterations in cancer specimens to facilitate diagnostics research

- Development, improvement or adaptation of DNA based technologies for application to diagnostics research, including chip technologies, DNA sequencing, hybridization, biochemical or enzymatic degradation and other technologies using genes, pieces of genes or other DNA sequences

- Development, improvement, or adaptation of technologies to measure gene expression patterns as they relate to diagnosis and prognosis, including chip development or other technologies to immobilize RNA on a solid matrix and any technologies based on quantitation of RNA, differential display, or RNA sequences

- Development of technologies to identify changes in protein composition, structure, or expression as they relate to diagnosis and prognosis. Proteins include hormones, hormone receptors, tumor suppressor genes, oncogene products, members of metabolic pathways, cell structural protein, or other proteins involved in cancer initiation and progression

- Development of technologies to identify alterations in other cellular components not identified above for use as diagnostic and prognostic markers of cancer or for the staging of tumors

- Development of informatics systems to manage large sets of data generated by high-throughput molecular diagnostic technologies, including development of systems for the correlation of clinical and experimental data

- Development of expert systems, artificial intelligence, or neural networks specifically for improvement of tumor diagnosis, classification or prognosis

- Development of semi-automated, automated or robotic systems that facilitate high-throughput analysis of tumor specimens, including integrated systems for tissue sample preparation, sample analysis and data collection

- Development, improvement or adaptation of instruments for diagnostic evaluation of tumor specimens, including magnetic resonance and other spectroscopic techniques

- Development or improvement of automated or semi-automated systems for analysis of single cells, cell classification or measurement of cell proliferation for cancer diagnosis

X. RADIATION THERAPY

- Clinical research in radiotherapy using ionizing and non-ionizing radiations and those areas in radiobiology and radiation physics that relate, in large part, to radiation therapy; laboratory studies including investigations at the molecular, cellular, tissue, and whole animal levels. Major scientific areas of interest include:

  Mechanisms of radiation injury and repair in normal and neoplastic tissues, especially those responsible for resistance

  Radiation modifiers, including sensitizers and protectors

  High LET radiotherapy-related research

  Boron Neutron Capture Therapy (BNCT)

  Radiological physics investigations pertaining to radiotherapy

  Use of new physical modalities or new uses of conventional physical modalities: hyperthermia alone or combined with radiation, UV, NMR, radioisotopes

  Combined modality research involving radiation therapy

  Use of radioactively labeled antitumor antibodies for the localization and therapy of cancer

  Tumor induction after cancer therapy

  All other studies related to radiation therapy

All clinical research in photodynamic therapy and those areas of photochemistry, photophysics and photobiology that relate, in large part, to photodynamic therapy.

XI. DIAGNOSTIC IMAGING

Support of investigation, development and evaluation of imaging in cancer diagnosis, treatment and follow-up. Support for research in the imaging sciences includes both hardware and software aspects, encompassing image acquisition, processing, transmission, manipulation and archiving for oncology.

- Imaging modalities: development, optimization, characterization and preclinical evaluation of representative modalities in all organ sites such as:

  X-Ray Imaging: Digital X-ray sensors including storage phosphors and real time imaging sensors, stereotactic X-ray sensors, X-ray Computed Tomography (CT), in vitro microscopic X-ray imaging

  Magnetic Resonance Imaging (MRI): MRI, functional fMRI, Magnetic Resonance Spectroscopy (MRS), Chemical shift Imaging (CS(), MRI perfusion/ diffusion, imaging of phenotype expression

  Nuclear Imaging: Positron Emission Tomography (PET), Single Photon Emission Tomography (SPECT) including coincidence detection, other novel planer or tomographic nuclear imaging devices

  Ultrasound Imaging: Transducer development and array design, 2D and 2D ultrasound, related endoscopy or microprobe devices

  Non-Ionizing Imaging Devices including: Infrared thermography, ultraviolet and optical imaging, devices including laser imaging and related holography, microwave and other imaging methods through the EM spectrum, including magnetic source imaging, bioelectric imaging and visible light imaging

- Contrast agents for improved tumor visualization, interpretation and treatment for cancer diagnosis, staging and treatment and understanding physiological states of organ and tumor systems

  Contrast agents for X-ray imaging, MRI and US imaging including organ and tumor specific agents

Radiolabelled materials for diagnosis and therapy to include antibodies and their fragments including ligands

- Imaging acquisition, display, hard copy, transmission and analysis, central and remote diagnosis, including related teleradiology and telemedicine applications

  Image Processing and Display: Image noise suppression, image restoration, image reconstruction methods, image segmentation, feature extraction for detection and classification of cancer, image registration/ compression and related image processing for image guided diagnosis and treatment including 2D and 3D methods, digital image acquisition and display techniques

  Image Display: Computer monitor displays and related software interface, hard copy displays, related computer networks for improved image interpretation transfer and analysis

  Image Perception: Analysis of image perception for different displays

  Information Technology Systems: Picture Archiving and Communication (PACS) systems, image management and decision making support systems, teleradiology and telemedicine applications systems for oncology imaging and general diagnostic radiology

- Interventional radiology and techniques utilized in image guided diagnosis and treatment

  The development of systems and techniques used in minimally invasive procedures

  Endoluminal stent-graft development

  Adaptation of existing technologies to image guided minimally invasive procedures

- Clinical evaluation of imaging methods, both emerging technologies and mature techniques

XII. CLINICAL TREATMENT

Clinical research studies designed to evaluate cancer treatment. This category includes all Phase I, II and III clinical trials using drugs and biologic agents, clinical trials in AIDS-related malignancies and gene therapy/marking trials. Preclinical studies that address specific issues related to the design of a clinical trial may be included in this category.

- All clinical trials in which chemotherapeutic and/or biologic agents are used as a major component of the treatment regimen. These studies may employ chemotherapy alone or in combination with radiotherapy or surgery.

- Clinical studies (including Phase I and early Phase II trials) which contain the following:

  In vitro or in vivo tests done to predict the clinical response to cytotoxic and biologic therapies
  Pharmacologic and immunologic monitoring of the agents (plasma and/or tissue)
  Modulation of drug toxicity and/or efficacy through chronotherapy
  Use of agents to reverse resistance to or reduce toxicity from the cytotoxic therapy
  Use of target specific delivery systems to enhance the selectivity and therapeutic effects of agents
  Establishment of dose-response relationship and efficacy

- Studies conducted with the intent of selecting patients for therapy and predicting response to specific therapies
  Pharmacology of drug synergism and multi-agent therapy
  Predictability, reversibility, and mechanisms of drug-induced toxicity in vitro and/or in vivo test systems to assess efficacy of therapy
  Assessment of drug resistance in human tumors; reversal of clinical drug resistance
  Assessment of prognostic factors (biological or molecular) that may predict response to specific treatment therapies

- Clinical studies to reduce the toxicity of cytotoxic therapies by the use of agents such as:
  Colony stimulating factors
  Radio/chemoprotective agents
  Agents that bind free radicals

- Clinical studies utilizing gene therapy and gene marking for tracking disease recurrence

- All types of stem cell and bone marrow transplantation in cancer patients

- Chemotherapy, immunotherapy, and stem cell and bone marrow transplantation for AIDS and HIV positive patients with cancer

- Clinical studies using biological response modifiers or biological approaches to cancer treatment, such as vaccines, immunotherapy, cellular therapy, antisense therapy, and liposomes.

- o Clinical studies using agents directed at subcellular target sites, including cell cycle targets, oncogenes, and suppressor genes.

- o Clinical investigation, including experimental design, computer programming and biostatistics, and radiological histopathologic and immunologic support

- o Supportive care programs emphasizing preclinical and clinical research studies which will improve the quality of life through supportive management of cancer patients undergoing antineoplastic treatment

- o Clinical trials using "unconventional therapies", including, but not limited to, behavioral and psychological approaches, dietary, herbal, pharmacologic and biologic treatments, and immuno-augmentative therapies (ref: U.S. Congress, Office of Technology Assessment, Unconventional Cancer Treatments, OTA-H-405; Washington, D.C.: U.S. Government Printing Office, September 1990)

XIII. NUTRITION

- o Nutritional assessment of the patient with diagnosed cancer

- o Methods - monitoring, assessing, and validating nutritional status and changes in these parameters

- o Definition of optimal nutritional status and requirements

- o Clinical relevance and comparison of nutritional parameters

- o Special assessment problems unique to cancer population

- o Body composition studies

- o Anthropometrics and other physical methods

- o Biochemical and metabolic assays

- o Nutrient intake data pertaining to clinical trials involving cancer patients

- o Treatment effects on assessment parameter(s) or techniques

- o Etiology and pathogenesis of malignant anorexia

- o Sensory abnormalities, e.g., taste, smell, etc.

- o Central mechanisms, neuroendocrine hormones, etc.

- Peripheral mechanisms
- Physical abnormalities, e.g., oral, gastrointestinal toxicities
- Tumor metabolism - relationship to host
- Treatment effects on host and tumor metabolism
- Psychologic aspects, e.g., food aversions, tolerance of nutritional support
- Nutritional intervention in the patient with diagnosed cancer
- Nutritional supportive mangement; prevention or treatment of deficiencies or toxicities resulting from cancer therapy or malignancy that adversely affects nutritional status; preservation of quality of life
- Maintenance of nutritional status
- Determination of "ideal" population for nutritional support
- Preclinical and clinical trials - improvement of current methods:

    Routes of administration
    Tailoring support to special needs
    Duration: short-versus long-term support
    Study design: feasibility, patient accepance, cost-effectiveness

- Correction of nutritional status
- Appetite stimulation (behavior modification, physical or pharmacologic methods)
- Anti-catabolic therapy (anabolic steriods, exercise, etc.)
- Improved ability to eat (anti-emetics, treatment of mucositis, etc.)
- Correction of specific nutritional abnormalities or deficiencies
- Nutrition and nutrients as treatment for cancer

    Role of nutrition and nutrients in the direct treatment of neoplasms, alone or in combination with other modalities

    Nutritional modulation through dietary or supplemental modification

Nutritional elements, including: whole diets or foods, macronutrients (i.e., fat, protein), vitamins, minerals, and co-factors, and food additives (natural or synthetic products normally associated with dietary sources)

- o Preclinical and clinical toxicity studies-physiologic or pharmacologic doses
- o Efficacy of nutritional therapies:

  Augmentation of non-nutritional modalities, e.g., radiation, chemotherapy

  Interactions of nutrients with chemotherapeutic drugs

  Therapeutic efficacy of nutrient-combination regimens

- o Improved treatment based on nutritional requirements of tumor vs. host
- o Nutrient-deficient or nutrient-inhibitor regimes
- o Nutritional modulation
- o Use of nutrition and nutrients to reduce complications not directly related to nutritional status:

  Improvement of immune and bone marrow function (e.g., neutropenia, infection)

  Prevention of major organ toxicity, e.g., antitoxidant effects, etc.

  Reduction of surgical complications, e.g., engraftments, wound healing

XIV. SURGICAL ONCOLOGY

- o Intervention studies in which surgery is the dominant feature to prevent, diagnose, stage, or treat cancer; all surgical specialties, except neurosurgery and eye surgery, are included
- o Special devices for dividing or destroying tissues, such as cryosurgery, laser surgery, or ultrasonic surgery; other studies in which surgery is the prominent feature in vascular access, dearterialization, hyperthermia, or infusion/perfusion with biological or chemotherapeutic agents
- o Development and improvement of instruments for detection and diagnosis of tumors where surgery/biopsy is the dominant feature of the process

- o Cytoreductive procedures, intraoperative radiotherapy, surgical treatment of cancer complications, surgical supportive care, and plastic reconstructive and rehabilitation surgery

XV. CLINICAL TRIALS (U10s)

The NCI's Clinical Cooperative Groups consist of researchers who jointly develop and conduct cancer treatment clinical trials in multi-institutional settings. They are a major component of the extramural research effort of the Division of Cancer Treatment. Each Group is supported to continually generate new trials compatible with its particular areas of interest and expertise, as well as with national priorities for cancer treatment research. Unlike most other major NIH cooperative clinical trials efforts, Group structure and funding are not usually linked to any specific clinical trial(s). This mechanism thus has the potential for considerable flexibility in resource allocation, and for the rapid testing of promising new cancer therapies in large patient populations, since the apparatus for conducting such trials is constantly in place.

XVI. BIOCHEMISTRY AND PHARMACOLOGY

Preclinical studies designed to improve cancer treatment; emphasis is on discovery of new drugs and treatment strategies, selective targeting, development of new preclinical models, and understanding, preventing, and overcoming drug resistance. Studies must demonstrate obvious relevance to therapy.

- o Biochemical and molecular mechanisms of antitumor drug action

  Drug-induced tumor inhibition, apoptosis, cytotoxicity, and differentiation

  Anti-metastatic/anti-angiogenesis therapy

  Drug transport systems

  Effects of agents on subcellular target sites:

    DNA, RNA, and protein synthesis; transcription/ translation factors
    Cell membranes
    Cell structural proteins such as microtubular proteins
    Chromatin and chromosome structure; gene amplification
    Gene and oncogene activation/suppression
    Membrane or intracellular receptors; cell cycle; cell signaling systems; ion fluxes

Modification of macromolecules: phosphorylation, methylation, conjugations such as myristylation and isoprenylation, crosslinking, DNA repair, etc.
Intermediary metabolism
Key enzymes (e.g., topoisomerases).

Drug and xenobiotic detoxifying mechanisms

Modification of enzymes or other drug target sites by site-directed mutagenesis or genetic engineering techniques

Molecular biology and biochemistry of drug resistance

Chemotherapy directed against growth factor synthesis, degradation or function

- Pharmacology of antitumor drugs

Quantitative and qualitative aspects of drug disposition; plasma tissue levels, drug metabolism and excretion; transport of anticancer agents

Pharmacokinetics of single agents or combinations

Target-specific cytotoxic drug delivery using liposomes or other carrier systems

Drug-antibody conjugates

Drug-drug and drug-irradiation interactions

Modulation of drug action to increase activity or decrease toxicity

- Toxicology of antitumor agents

Pharmacologic and pathologic data required for the design of active but less toxic agents

Improved in vitro or in vivo test systems for prediction of potential toxic effects

Mechanism of action of drug-induced tissue damage

Physical and chemical rescue strategies to reduce normal tissue damage

- Anticancer screening and experimental therapeutics

Development of novel or improved laboratory models predictive for clinical efficacy

Development of anti-metastatic/anti-angiogenic models for therapeutic studies

Development and use of transgenic/knockout/gene replacement models for drug studies.

Combination drug therapy or adjuvant therapy

Dose-response, scheduling, and route of administration studies

Cell cycle kinetic studies

Drug resistance: strategies to prevent or overcome resistance; cross resistance studies; drug screening with resistant cells

Chemotherapeutic agents in combination with biological response modifiers, antibodies, or radiotherapy

Selective toxicity against tumors

Novel strategies, such as extracorporeal treatment

Novel therapies to modulate drug action

Preclinical anticancer gene therapy studies with therapeutic intent

Identification, characterization and exploitation of oncogene/suppressor genes or their products as potential drug targets; identification, characterization, and exploitation of other novel molecular drug targets

o Natural products drug discovery and development

Isolation, characterization, and evaluation of potential antitumor agents from microbial, plant, fungal, or animal sources

Production of compounds of high program interest not available in adequate quantities from natural sources by: total synthesis, tissue or cell culture; modification of chemical ecology of producing organisms; transgenic systems; production of compound libraries

Ethnopharmacological investigation of cancer treatment in traditional systems of medicine and evaluation in experimental systems

o Anticancer drug synthesis and evaluation

Design, synthesis, and evaluation of rationally-selected analogs of key molecules, including antisense oligonucleotides, lipids, peptides, growth factors, hormones, and nucleotides

Rationally-designed syntheses and testing of analogs of new active synthetic compounds or natural products; structure-activity relationships and development of combinatorial libraries

Computer modeling and structural studies aimed at improving design of new anticancer drugs

Synthesis and pharmacology of prodrugs, latent drugs, and modifiers of cancer drug metabolism or excretion

Genetic technology approaches to discover and develop more efficacious cytotoxic agents

- o Enhancement of efficiency of drug discovery and development

  Design of computer software to make drug screening and other drug development steps more efficient and the data easier to access and analyze via electronic means

  Development of automation/robotics to make drug screening and other drug development steps more efficient

  Computer modeling to reduce animal use in drug screening, pharmacokinetics, etc.

  Development of novel ways to analyze large biological and chemical data bases using neural networks or other advanced computing techniques

  Development of new technologies for optimal imaging of sources of natural products to assist in identification of materials

XVII. BIOLOGICAL RESPONSE MODIFIERS (BRMs)

Discovery, testing and development of biological response modifiers (BRMs) for the treatment of cancer. BRMs are agents that alter the relationship between the tumor and its host by modifying the host's biological response to tumor cells with resultant therapeutic benefits. The BRM program supports preclinical and pilot studies using human subjects that focus on the mechanism(s) of action of biological agent(s) in order to explain the antitumor effects and to understand the basis of the observed toxicities.

- o Examples of BRMs of interest for cancer therapy development include:

  Adjuvants: bacterial, fungal, or cellular

Antibodies: heteroantisera or monoclonal antibodies, produced by any means against tumor specific or tumor-associated antigens or against viral associated or normal tissue antigen shared by tumor cells or against one or more subpopulations of cells of the immune system, unconjugated or conjugated to radioisotopes, toxins or chemotherapeutic drugs, in natural form or hybridized

Antigens: tumor-associated or tumor-specific cellular antigens, viral associated antigens, normal cellular antigens, synthetic or natural immunogens, chemically altered antigens, somatic cellular hybrid antigens, and virogene products (includes the use of viral components to augment the immunological destruction of tumors)

Cytokines: examples include the interleukins, colony stimulating factors, growth and maturation factors (includes both specific and nonspecific growth factors with both direct and indirect antitumor effects), tumor necrosis factors, etc.

Interferons

Thymic factors: examples include thymosin, thymopoietin, thymic humoral factors, etc.

- Examples of biological approaches to cancer treatment that are of interest include the following:

  Cellular therapy: use of either unfractionated or purified cells with anticancer potential, such as, T-cells, B-cells, NK-cells, LAK-cells, macrophages or monocytes, either inactivated or activated to specifically or nonspecifically kill cancer cells

  Antisense therapy: oligonucleotides (DNA, RNA) that can be used to inhibit oncogenes or oncogene products, growth factors coded for by oncogenes, whether secreted or intracellular; inhibitors and factors regulating expression

  Liposomes: use of liposomes encapsulated with BRMs in antitumor studies

- Research that utilizes BRMs for cancer treatment can be illustrated as follows:

  Discovery and development of BRMs (production, assay, isolation, and characterization) from natural sources, cell lines or recombinant DNA sources when the primary intent is production of BRMs for the evaluation of their therapeutic potential in anticancer and anti-AIDS models

  Development and application of assays to monitor efficacy of BRMs in cancer treatment

Evaluation of preclinical model systems for predicting therapeutic benefits of BRMs; preclinical pharmacology of BRMs, including toxicity, pharmacodynamic modes of elimination, body fluids, tissue distribution, and effects on metabolism; species variability and dose response relationships

Studies of mechanisms of action of BRMs in preclinical and pilot studies using human subjects, when these studies are an integral part of an overall research project to develop biological agents for cancer therapy. For example, BRM effects on cytokine production, immunostimulation by antigens, immuno-restoration, immuno-suppression, development of cell-mediated cytotoxicity, and the effects on cell subpopulations in the context of therapeutically oriented studies. Such studies are considered important for determining the mechanism of action and overall therapeutic potential or value of BRMs.

Development of BRM reference standards for use in standardizing assays used to monitor therapeutic trials and other investigations

BRMs in combination with conventional chemotherapy, toxins, or radiotherapy

Development of various targeting molecules, such as peptides or monoclonal antibodies (e.g. murine, chimeric, human, bifunctional, anti-idiotypes, etc.) and their fragments for cancer therapy. These reagents may be conjugated with various ligands, including radionuclides, chemotherapeutic agents, or toxins which depend upon the targeting molecule and its properties for effective cancer therapy. Included in this list of targeting molecules are genetically engineered agents which may be fusion molecules of more than one BRM.

Antisense oligonucleotides, including DNA, RNA, and ribozymes for the inhibition of certain growth factors, receptors, and cytokines resulting in an antitumor response

Biochemical modification of BRMs with therapeutic effectiveness in cancer to determine the molecular basis of the anti-cancer activity

Use of bone marrow, when treated with BRMs prior to or after transplantation to remove contaminating cancer cells; of fetal thymic and/or liver transplants with BRMs for cancer therapy

Use of cytopheresis, plasmapheresis, or immunoabsorption of inhibitors (i.e., antigen, blocking antibody, complexes, suppressor factors or cells, etc.) of antitumor systems (cellular or molecular)

Immunization with chemically altered or virally infected tumor cells or cell extracts, and immunization with somatic cell hybrids of tumor and normal cells; immunization with transfected tumor cells or with peptide antigens; use of genetically altered tumor cells or immune effector cells in active or adoptive immunotherapy

XVIII. BIOMETRY

- Development and application of new biostatistical methodologies to support studies in cancer etiology, including but not limited to medical, environmental, occupational, lifestyle, dietary, demographic, genetic factors, and joint effects or interactions of two or more of these factors

- Development of biologically-based statistical models for quantitative cancer risk assessment, taking into account age and/or duration of time with exposure to single, multiple, or potential interactions of combined carcinogens

- Statistical techniques to support cancer-related epidemiological studies and clinical trials, for example:
  - survival analysis
  - risk assessment
  - meta-analysis
  - cluster and spatial analyses
  - multiple endpoints
  - multiple arm trials
  - genetic epidemiology methods
  - repeated measures
  - missing data
  - misclassification
  - dose-response
  - left and right censoring
  - sampling
  - environmental epidemiology methods
  - molecular epidemiology methods, including biomarker analyses

- Development of statistical methods incorporating computer technology into cancer-related studies, such as for bioinformatics, multiple database linkages, geographic-specific models, geographic information systems, and reconstruction of environmental exposures

XIX. GENETIC EPIDEMIOLOGY

- Epidemiologic studies of genetic factors related to cancer risk, such as:

  Identification of cancer susceptibility genes through segregation, aggregation, and linkage approaches

Identification and study of cancer-prone families through the establishment of extended cancer-related pedigrees with specimen repositories

Loss of heterozygosity studies to suggest candidate regions for cancer-related genes and to identify high-risk population subgroups

Interdisciplinary studies to identify and establish the association between cancer genes and precancerous lesions or invasive cancer

Evaluation of the role of gene-gene and gene-environment interactions in cancer etiology

Evaluation of the feasibility and validity of suspected genetic markers in healthy human populations

Determination of prevalence and penetrance of identified genes in the general population

- Genetic testing for inherited cancer susceptibility genes in human populations:

  Strategies for counseling and measurement of impact and effectiveness of counseling on testing decisions

  Mechanisms and methods for obtaining informed consent and assessment of the adequacy and changing needs

  Evaluation of behavioral and psychosocial responses to testing

  Determination of psychosocial impact of availability, use, and non-use of genetic testing of high-risk family members

  Methods to minimize psychosocial harm and maximize benefits

  Measurements and determinations of extent of discrimination against individuals tested in research and clinical settings

  Descriptive studies of influential sociodemographic characteristics and impact of testing

  Strategies and guidelines for preservation of privacy regarding genetic testing

XX. POPULATION-BASED AND MOLECULAR EPIDEMIOLOGY

- Studies in human populations and population subgroups of:

  Natural history of neoplasia, including the role of precursor lesions and preneoplastic conditions

  Incidence, prevalence of, and mortality from human cancers, including cross-cultural distributions and time trends

  Geographic-related cancers and national or international trends with respect to one or more potential risk factors

- Etiologic studies of human cancers, including application of markers for:

  Intrinsic, other than heritable- factors, and host-specific risk or protective factors, including carcinogen metabolizing enzymes

  Environmental and life-style factors, including
  - Tobacco products
  - Alcohol
  - Diet and nutrition
  - Medicinal agents
  - Infectious agents, including viruses
  - Trauma
  - Physical activity
  - Occupational or recreational hazards
  - Environmental pollution
  - Suspected or unknown environmental and chemical carcinogens

  Reproductive factors

  Cultural/behavioral characteristics

- Methodological studies related to human cancer, such as:

  Development and validation of improved methods of measuring cancer susceptibility, exposure to carcinogenic materials, and joint effects of risk factors

  Development of population-based methods to evaluate causal associations or mechanisms of carcinogenesis in human populations

  Development of research technology or tools for differentiating and characterizing socio-behavioral, cultural, demographic and lifestyle profiles of high-risk and understudied human populations

  Assessment of relative contributions of environmental agents in combination with genetic-related factors, including potential interactions

Assessment of risks attributable to specific factors, to guide the development of preventive strategies

- Special emphasis areas associated with cancer outcome

Biochemical/Molecular Epidemiology

Elucidation of molecular biology processes as potential markers related to the natural history of neoplasms in human populations

Identification and assessment of innovative, exploratory laboratory-based measurements and/or markers (genetic, molecular, cellular, tissue, organ levels) that can be utilized in epidemiologic studies of cancer etiology

Development and validation of applicable biomarkers of risk (e.g., carcinogenic dose exposures in target tissue, individual variability in metabolic polymorphisms), surrogates of early stages of environmental carcinogenesis, and measurable confounder variables

Application of markers for quantitative estimations of cancer risk in general populations or in cohorts with varying levels of exposure to potential risk factors (viz. environmental/occupational chemicals, physical agents including ionizing and electromagnetic field radiation, and diet/lifestyle)

Identification and development of markers of acquired susceptibility with potential usefulness for large scale epidemiologic studies

Evaluation of etiological role (i.e., association, effect, influence) of interaction, synergy, or antagonism of combined risk markers, such as environmental exposures and carcinogen metabolizing enzymes

Application of new technological advances in cellular and molecular methods for utilization of biological specimens in population-based epidemiologic studies

Infectious Disease/AIDS-Related Epidemiology

Studies of the natural history of cancers and preneoplastic conditions associated with biological agents, primarily viral but also including bacterial, fungal, protozoal agents, and other microscopic forms of life

Elucidation of the eitologic role of oncogenic and/or suspected oncogenic biological entities, including viral oncogenes, and viral gene products. Examples include, but are not limited to: AIDS/HIV,HTLV-I/II,EBV,KSHV/HHV8,HPV, hepatitis viruses,SV40,JC and BK viruses, polyoma viruses, adenoviruses, endogenous human retroviruses, Helicobactor pylori, and human infections with animal viruses such as bovine leukemia virus and simian T-cell lymphotropic virus

Assessment of oncogenic potential of emerging or re-emerging infectious agents

Investigation of the role of infectious agents in cancer induction during acquired host immuno-deficiency (e.g., result of retroviral infection or organ transplant): Kaposi's sarcoma, adult T-cell leukemia and lymphoma, EBV-associated Hodgkin's Disease, KSHV-associated lymphoma, viral-associated non-Hodgkin's lymphoma, H. pylori associated malignancies, infectious disease-associated central nervous system tumors

Clinical Epidemiology: Clinical Populations

Epidemiologic studies of the natural clinical history of conditions predisposing to human cancer, precursor lesions and invasive neoplasms

Identification of molecular and clinical markers of cancer risk, cancer recurrence, prognosis, and clinical outcomes related to survival

Identification of factors modulating cancer risk, recurrence, prognosis or clinical outcomes related to survival

Assessment of the effectiveness of socio-behavioral, environmental, medical, and health policy-related interventions in altering natural history (clinical outcomes)

Technical and methodologic approaches for defining risk factors or confounders of cancer risk in terms of their impact on adverse health effects

Endocrinologic Epidemiology

Evaluation of relationship between hormonal factors (endogenous and/or exogenous), products/ pathways of hormonal metabolism, or hormone-like environmental chemicals and cancer development

Determination and assessment of the role of hormone receptors in cancer development and progression

Analyses of joint effects and interactions between hormonal status/factors and genetic-related, environmental (including diet and lifestyle), or time/age-related events and cancer risk

Assessment of the role of preclinical events, endocrine factors, environmental, and genetic influences in human populations with contrasting cancer risk and differing risk factor profiles, such as for, but not limited to, hormone-related cancers

Research Ethics in Epidemiologic Research

Process or outcome studies involving protection of human subjects, including:

- issues in informed consent
- security and confidentiality of sensitive information
- use of stored tissue samples
- inclusion of women and minorities
- recruitment of subjects with special needs or requirements (e.g., children, cognitively impaired)
- legislative research mandates

XXI. PREVENTION

Research studies to identify, evaluate, and implement techniques and approaches for the prevention and early detection of cancer with minimal risk and cost, including:

- Chemoprevention - studies related to the identification and evaluation of agents that may inhibit carcinogenesis, i.e. initiation, promotion, transformation and/or progression of the malignant process as presently understood.

  Identification through epidemiologic studies or literature searches of agents considered appropriate for further evaluation

  Identification and characterization of potential agents by *in vivo* and/or *in vitro* laboratory methods

  Efficacy and toxicology studies of agents in animals to elucidate promising ones for further human studies

  Phase I, II and III intervention clinical trials of potential chemo-preventative agents. A phase I trial is typically a small study that determines the safe dose range, basic toxicological profile, and pharma-

cological characteristics of the agent. Phase II trials usually involve the evaluation of biochemical or biological markers as intermediate endpoints as part of the determination of effective doses and further toxicology studies. Pilot studies of trial designs utilizing these intermediate marker tests are risk reduction, double-blind intervention studies. Phase III trials are typically larger randomized studies in the target populations.

- o Nutrition and diet

  Role of dietary patterns, foods and nutrients or other dietary components in cancer incidence and prevention. Influence of dietary factors on the modulation of cancer risk markers (including genetic markers), early indicators of cancer risk or intermediate endpoints. Biochemical, molecular and other mechanisms by which dietary components may act as metabolic effectors that protect, control, decrease or increase cancer risk. Absorption and metabolism of nutrients and other dietary components associated with cancer risk and prevention. Clinical trials of dietary modification for cancer prevention or risk reduction. Dietary assessment in human intervention trials. Development of biochemical or biological markers for dietary compliance and exposure. Improved nutritional and dietary assessment instruments, including nutrient databases. Development of reliable methods for analysis of nutrients, other dietary components and their metabolites in foods, body fluids, and tissues

XXII. COMMUNITY ONCOLOGY

- o Introduction, application, and evaluation of effective and practical cancer prevention, control and rehabilitation intervention programs in community settings. The involvement of community physicians, nurses and other professionals in cancer control efforts and promotion of linkages between community practitioners/hospitals and other regional resources for cancer control are major goals. The primary objective is to stimulate research that will provide a basis to reduce the time between research advances in prevention, screening, early detection, patient management, continuing care, and rehabilitation and the application of those advances in community settings. Of particular interest are the following areas:

  Adoption of state-of-the-art prevention and treatment, including dissemination to underserved populations and geographic areas

  Use of symptom management, including pain control and palliative care

Prevention of adverse reactions to risk notification, genetic testing and treatment, including effects on quality of life and sequelae, both physiologic and psycho-social

Improvement of strategies to recruit minority participants in cancer prevention clinical trials

Improvement in compliance with prevention and treatment protocols

Development of techniques to maintain and restore physical and psycho-social functioning during treatment and during long-term follow-up

Assessment of the cost/benefit ratio and/or cost-effectiveness of cancer prevention and management activities

Utilization of the home as a setting for care

Development and evaluation of community-based participation in up-to-date cancer management activities

Utilization of interventions to foster best possible functioning, physical and psycho-social, of the patient and of the cancer survivor

- o Patterns of physician and other health care provider activities in the area of cancer prevention, early detection, and management

XXIII. HEALTH PROMOTION SCIENCES

Development and testing of intervention strategies to modify personal, social, and lifestyle factors known to contribute to the development and/or increased risk of cancer; primary prevention efforts in nutrition and smoking, using schools, worksites, physician practices, and communities as intervention sites; secondary prevention projects in cervical, breast, colon, and skin cancer screening.

XXIV. EVALUATION AND CANCER CONTROL OPERATIONS RESEARCH

Mathematical and computer techniques for the analysis of data obtained from cancer control intervention studies.

XXV. SPECIAL PROGRAMS

- Smoking, Tobacco and Cancer Program

  Intervention activities aimed at reducing cancer incidence related to smoking and tobacco use. Primary interest is in research on interventions in cancer control Phases IV and V to prevent tobacco use, onset or habitual use. Research on methods and strategies that merely identify more efficient ways to control tobacco use are not encouraged.

- Special Populations

  Multidisciplinary intervention research aimed at addressing and modifying the excessive cancer incidence and/or mortality rates, lower cancer survival rates, or inadequate cancer prevention and control services for special populations. The term "special populations" refers to those population segments which may experience, or are known to experience, high cancer rates and/or are undeserved in terms of cancer prevention and control programs. Special populations include Alaskan natives, American Indians, Hispanics, Asian-Americans, Blacks, blue-collar groups, the elderly, lower-income groups, native Hawaiians and American Samoans. The phases of cancer control research differ from those chemoprevention studies, and phases II through IV are especially relevant. Phase II studies test ways in which existing intervention methods can be used or adapted for special populations or studies of new methods designed to be sensitive to the needs of special populations, or methodological research on validation of assessment instruments in special populations. Phase III and IV intervention research is aimed at primary and secondary prevention strategies that identify factors leading to avoidable cancer mortality and develop interventions to alleviate these factors through control of tobacco use and/or changing patterns of medical care use and delivery.

XXVI. PUBLIC HEALTH APPLICATION RESEARCH

The Public Health Agency Program is an active effort to involve the public health community in the development of initiatives and programs for cancer risk reduction and cancer prevention and control. The program seeks to involve State and local health departments in research and demonstration programs consistent with the Cancer Control Objectives for the year 2000.

Primary interest is in (1) research on interventions in cancer control Phases IV and V in public health settings, and (2) the dissemination and application of research findings among public health agencies and professionals. Focus is on tobacco prevention and control, breast and

cervix screening tests and other proven cancer screening tests, dietary interventions and cancer related environmental/occupational interventions. Areas of interest include:

- o Development of methods for delivering proven cancer prevention and detection in public health settings including clinics, hospitals, and health promotion centers.

- o Development of methods for the coordination and delivery of cancer prevention and control in public health areas through multiple intervention channels including but not limited to schools, worksites, health groups, and community agencies

- o Analytic studies of state and local cancer morbidity and mortality data for use in targeting and monitoring public health interventions

- o Analytic studies of state and local policy developments in cancer prevention and control and the effects of policies on practice

- o Capacity building in public health agencies and training of health professionals to ensure the delivery of appropriate cancer prevention and control to large populations

- o Development of models for joint cancer center/schools of public health/health agency collaboration to further cancer prevention and control in defined geographic areas

- o Ensuring the dissemination and application of tested methods for cancer prevention and control in public health settings

XXVII. SURVEILLANCE

Data collection, statistical analysis and mathematical modelling, and information data base linkage studies are required to monitor progress toward cancer control, particularly as it pertains to national goals. Methodology studies, validation and reliability studies, and research to improve comparability of data bases and response rates, including those which may be a prelude to large-scale data collection and survey activity, are included. Supplemental studies designed to enhance interpreting and assessing cancer control regional and national programs are important adjuncts to on-going survey research.

Three application areas are highlighted.

- o Surveillance of national nutrient and dietary information at both the individual and societal

levels, including food supply indicators, institutional policy and practices, consumer attitudes and behavior, knowledge and eating patterns related to health and disease, and dietary validation methodology for measuring nutrient intake and predicting eating patterns

- o Assessing the extent to which state-of-the-art cancer treatment is practiced nation-wide, defining optimal care across the age spectrum, creating appropriate indicators of cancer care, developing methods for accessing patient care information and the cost of care, and identifying pathways to care, barriers to optimal care, and the patient/physician/payer decision-making process and policies that influence treatment choices

- o Evaluation and cancer control operations research studies; mathematical, statistical, operations research, and computer information technology for the analysis, encoding, data reduction and interpretation of data obtained from cancer control intervention studies; mathematical modelling, particularly for resource allocation, decision-theory applications, and simulation studies relevant to cancer control; analytic studies designed to assess program impact and trends (current and projections for the future), in cancer statistics, particularly the inter-relationship of primary measures of the cancer burden (e.g., case, deaths, incidence and mortality rates, survival, etc.)

XXVIII. EARLY DETECTION

Development of scientific information and concepts and dissemination of knowledge regarding early detection techniques, practices, and strategies to reduce mortality and morbidity from cancer. The program supports clinical trials and other appropriate research, fosters technological development, and encourages the publication of scientific findings and adoption of early detection practices. Areas of specific interest include:

- o Outcome measures, surveillance methodologies, and analytic techniques relevant to early detection:

  Meta-analysis and survival analysis of early detection/screening clinical trials

  Cancer mortality and survival studies as related to early detection

  Intermediate endpoint studies in regard to effectiveness of early detection

- Identification, development, and evaluation of clinical technologies relevant to early detection:

  Cellular, molecular and genetic tumor markers (e.g., mutation, clonality, amplification)

  Molecular epidemiology and genetic risk factors

  Imaging technology

- Transfer basic laboratory findings into applications in early detection with the goal of extending this research to comparative clinical trials

- Development and evaluation of new early detection techniques and measure sensitivity, specificity, predictive value, validity, and safety

- Promotion of the linkage between laboratory and applied sciences to support the transfer of new technologies for early detection

- Promotion and dissemination of cancer and cancer detection information through graphic programs including maps and other educational material

- Identification, evaluation and implementation of computer systems for tracking and follow-up in cancer screening, surveillance, and promotion of early detection principles and practices

- Analytic techniques to identify populations that may be at increased risk as indicated by genetic and metabolic phenotypes (susceptibility markers)

- Screening and early detection of cancer

  Research to significantly reduce cancer morbidty and mortality through early detection. Among the research areas of special interest are:

  Analyses of long-term follow-up data from completed studies for potential new interpretations based on the passage of time

  Determination of the cost/benefit or risk/benefit ratios of cancer screening and detection methods when applied in defined or target populations

  Identification and testing of strategies to decrease the rates of false-positive and false-negative findings associated with cancer screening and detection interventions when applied in defined or target populations

Primary care intervention studies comparing methodologies to implement early detection strategies in clinical settings

Identification of markers of risk, exposure, and pre-malignant events of progression that can be used to identify subpopulations at particularly high risk of developing cancer; this would enable targeted screening strategies or early intervention approaches

- Development of mathematical models, including neural networks and other simulation techniques, to predict prognosis based on early detection practices

AREAS OF OVERLAP

The National Cancer Institute has overlap situations with every other Institute within the NIH as well as with some other PHS agencies. In general, the mission of the NCI includes studies of the biology, detection, diagnosis, treatment, etiology, epidemiology, prevention and control of all types of cancer. Specific NCI overlap situations are summarized by Institute and PHS agency below:

AA - Associations between alcohol use or abuse and cancer are of interest to the National Cancer Institute as well as the NIAAA. Dual assignments to CA and AA are appropriate. When the research is to study alcohol as the primary etiologic agent of cancer, AA should be primary and CA secondary.

AG - CA should receive primary assignment when elderly populations are utilized in studies of cancer etiology, prevention, or epidemiology. This includes work toward identifying risk factors for cancer, identifying factors/agents for lowering cancer risk, and the statistical and data management methodologies to support such studies. When the focus is on understanding or modifying psychosocial risk factors for cancer in old age, AG should receive primary assignment.

CA should receive primary assignment when the emphasis is on elderly populations' response to and tolerance of cancer treatment or prophylaxis. This includes diagnosis studies and preclinical and clinical cancer prevention/treatment studies in chemoprevention/chemotherapy, radiotherapy, biological response modifiers, and surgery. CA should receive primary assignments in all aspects of diagnostic imaging. Studies on how the aging process may be affected by cancer or cancer treatment would be assigned AG primary.

Any preneoplastic or tumor cell study where the emphasis is on understanding the cancer process and/or its prevention or biology should be given CA primary assignment.

When the major thrust of research is the development, implementation and/or evaluation of methods or interventions to affect the cancer statistics of elderly populations or the health services utilization of elderly populations, particularly when the focus is on minority populations, primary assignment should be to be CA.

AI - BOTH CA AND AI HAVE INTERESTS IN APPLICATIONS IN THESE AREAS.

The development of control measures, such as vaccines and/or immunotherapeutic approaches, is of programmatic interest to both CA and AI. AI should receive primary assignment for applications focused on the development of vaccines against infectious disease. CA should receive primary assignment for applications focusing on basic, applied, or clinical research, including those conducted in animal model systems,

aimed primarily at the development of vaccines against neoplastic conditions. These studies may include microbial agents that initially produce infectious disease, but when the intent of the vaccine is to prevent malignant disease studies should receive CA primary assignment. The types of agents involved may include HPV, HBV, HCV, HIV, EBV, and H. pylori.

CA should receive primary assignment whenever the research involves studies of immunology directly related to host resistance, response to cancer and/or cancer therapy. These include all studies of immune responses to tumor cell targets and of the distribution and function of cell surface molecules on tumor cells. CA should also receive primary assignment for basic research on immunologic mechanisms considered to play a role in host resistance to cancer, e.g., natural killer cells, cytotoxic T cells, tumoricidal macrophages, lymphokine-activated killer cells. Some areas, such as cytotoxic T lymphocytes, macrophages, and programmed cell death are of interest to both AI and CA, and should be referred according to the significance and long-term goals of the study. CA and AI should be given dual assignment, with AI primary, in areas of immunology most relevant to infectious disease and allergy e.g., B-cell function, antibody structure and function.

CA should receive primary assignment on basic studies of bone marrow transplantation as treatment for leukemia or for immune reconstitution following high-dose chemotherapy or radiation. Other studies of basic immunology should be dually assigned to CA and AI, with primary assignment based upon the significance, aims and objectives of the study and/or patient population being used, e.g., immune reconstitution by bone marrow transplantation, immune suppression, tolerance, and immunological aspects of hematopoiesis.

CA should receive primary assignment when the research deals with biological agents (bacteria or viruses) as possible etiologic factors or cofactors in cancer and the control of these agents and their associated diseases. These studies include bacteria, viruses, viral products, related cellular products, tumor-inducing agents and resulting antibodies with known or suspected potential for oncogenic sequelae in animals or man (e.g., retroviruses, HTLV-I, HIV, SIV, hepatitis B virus, papillomaviruses, herpesviruses). CA should receive primary assignment for epidemiologic studies of the relationship between infectious agents (bacteria or viruses) and risk of cancer or of precursor conditions, such as cervical dysplasia, gastric dysplasia, carcinoma in situ, and intraepithelial cancer.

CA should be given primary assignment whenever the major aim is a linkage between an infectious agent and cancer or the research primarily concerns mechanisms of oncogenesis. This includes research proposed for primary treatment of microbial agents (viruses and bacteria) known to cause cancer. AI should have primary assignment for all basic

laboratory investigations leading to the development and laboratory evaluation of an AIDS vaccine when the primary goal of the vaccine is to prevent HIV disease or reduce viral replication. CA should have primary assignment for studies involving clinical evaluation of candidate AIDS vaccines in humans and for clinical trials in ATEUs for AIDS-Kaposi's Sarcoma.

AR - In the area of skin and musculoskeletal malignancies where the primary thrust is clearly the biology, etiology, prevention, diagnosis, treatment or epidemiology of cancer, CA should be given the primary assignment. When studies of growth factors and peptide and steroid hormones and their effect on cell division, growth, movement, and migration use tumor cell systems, CA should be given a primary assignment. When other cell systems are used, CA should be given a secondary assignment.

DA - CA should be given primary assignment if the emphasis is on HIV-associated cancers and risk modification by drug abuse. BOTH CA AND DA HAVE INTERESTS IN APPLICATIONS CONCERNING TOBACCO USE

DC - When tumor cells are used as model systems for understanding normal or impaired function of the communication processes of hearing, balance, voice, speech, language, taste and smell, DC should receive primary assignment and CA secondary assignment.

DE - BOTH CA AND DE HAVE INTERESTS IN APPLICATIONS IN THESE AREAS.

CA should be given primary assignment when the emphasis is on oral cancers and related risk factors rather than on oral functions. Studies involving the etiology, biology, prevention, diagnosis, treatment, and epidemiology of cancers of the head, neck, and oral cavity should receive CA primary and DE secondary assignment. Studies that address pain or other side effects of treatment in the presence of cancer of the head, neck and oral cavity should receive a CA primary and DE secondary assignment.

DK - Studies of hematopoiesis should be dually assigned to CA and AI when the emphasis is on differentiation of lymphoid/ myeloid cells and development of immunologic function, especially when relevant to bone marrow transplantation. Basic hematology should be assigned to DK or HL as appropriate.

CA should receive primary assignment for studies that deal with the following topics: the role of oxygen radicals and other free radicals in carcinogenesis and tumor promotion; the inhibition/suppression of free radical carcinogenesis/ promotion; and the role of synthetic and biological

antioxidants such as vitamins A, C, E, carotinoids and amino acids and their derivatives, metabolites and analogs in chemoprevention.

DK should be given primary assignment in studies of hepatitis/cirrhosis when the research is directed at studies of liver enzymes/liver function as a result of the disease.

Studies on the oncogenic sequelae of hepatitis/cirrhosis should be given primary CA assignment.

Research proposing to study the etiology, biology, prevention, diagnosis, treatment and epidemiology of endocrine organ, gastrointestinal, biliary tract, liver, prostate or kidney cancer should be given a CA primary assignment when the focus is on the malignancy and a DK primary assignment when such research focuses on disordered endocrine regulation. Research to elucidate cancer treatment, etiology and/or organ specific effects on these systems should be CA primary. For example, studies on the mechanisms of cancer chemotherapy toxicity to kidney function should be assigned to CA. Epidemiologic studies to elucidate the evaluation of endocrine risk factors for cancer should be given CA primary assignment. Studies of obesity and cancer risk should be given a CA primary, including methodologic research to elucidate markers of dietary exposures related to cancer risk. Studies of benign prostate hypertrophy as a cancer risk factor or predisposing disease should be given dual DK/CA assignment.

ES - BOTH CA AND ES HAVE INTERESTS IN APPLICATIONS IN THE FOLLOWING AREAS: GENETICS, CHEMICAL AND PHYSICAL CARCINOGENESIS, MOLECULAR INTERVENTION/PREVENTION, MODULATION OF ENVIRONMENTAL CANCER, BIOMARKERS OF EXPOSURE/SUSCEPTIBILITY/EFFECT, AND MOLECULAR EPIDEMIOLOGY.

CA should be given primary assignment when the purpose of the application is to relate environmental exposures and risk factors with cancer development. This includes all research concerned with the induction, promotion, progression and prevention of carcinogenesis initiated by chemical or physical agents, including those derived from food or non-edible plant sources. CA should be given primary assignment when the study deals with the metabolism and mechanism of action of carcinogens of environmental interest. Studies of carcinogens of environmental interest, in which the major end point to be investigated is cancer, should be given a CA primary assignment except for screening studies, which should be given an ES primary assignment.

ES should be given primary assignment when the study deals with chemicals in the environment, the environmental hazards of chemical and physical agents and their general toxicological effects. CA and ES should be given dual assignment for studies to develop carcinogenicity/ mutagenicity test systems with CA primary when more basic mechanisms of carcinogenesis/mutagenesis are involved.

CA should be given primary assignment when basic studies on the etiology and/or prevention of neoplasia in aquatic species are proposed. ES should be given primary assignment when aquatic species are used as models for studying the general biological effects of environmental agents and their toxicities as they relate to health.

EY - Dual assignments should be made on studies of primary tumors of the eye or visual system, including research on the biology, genetics, or diagnosis of retinoblastoma and ocular melanoma. EY should receive primary assignment in research projects that may lead to a better understanding of normal visual system development or function and to means of preserving vision in these disorders. CA should receive primary assignment when the main emphasis is on risk factors, such as genetic predisposition, associated with the development of tumors, on biological and genetic properties of tumors (e.g., metastasis, angiogenesis, neovascularization, etc.) or on diagnosis, prevention, and treatment of tumors.

FD - Studies of development of vaccines for AIDS, and possibly related retroviruses, and development of diagnostic imaging techniques (NMR, SPECT, ultrasound, imaging agents) for malignancies should be assigned to CA as primary. Primary assignment should be given to FD when the proposal concerns safety of the technology in these areas.

GM - CA should receive primary assignment on all functional studies of interactions between preneoplastic and/or tumor cells and the immune system as well as basic studies of immune mechanisms known to play a role in rejection of tumors, e.g., natural killer cells, cytotoxic T-cells, tumoricidal macrophages, lymphokine-activated killer cells, differentiation factors, lymphokines, cytokines. These studies include structure and function of recognition, restriction and secondary adhesion molecules as well as consequences of immune system tumor cell interactions, e.g., membrane events, ion fluxes, protein phosphorylation, gene activation or repression, cell activation, secretion of functional molecules, cytotoxicity. AI and CA should receive dual assignments, with AI primary, on functional studies relevant to infectious disease and allergy, e.g., B-cell function, antibody structure and function. Studies of basic cell and molecular biology, using lymphoid or transformed cells only as model systems to investigate cellular processes representative of other normal cells, and not because they are functional parts of the immune system, are appropriately assigned to GM or dually to GM and AI. Studies on anticarcinogen/chemopreventive agent immunomodulation of premalignant states should receive CA primary assignment.

CA should have primary assignment on studies dealing with biology, biochemistry, genetics, molecular biology, etc. of cancer cells, transformed cells, cancer tissues, and their cell products. CA should receive primary assignments with

GM a possible secondary on studies emphasizing a comparison of normal and neoplastic cellular processes, component structures, etc. Studies of cell growth regulation, cell cycle (e.g., involving growth factors and their receptors, peptide and steroid hormones and their receptors, and their effects on cell division), cell differentiation, and cell movement and migration which do not use preneoplastic or tumor target cell systems should receive GM primaries and CA secondaries. Only when studies of cancer and transformed cell lines are designed with the obvious intent to investigate normal processes, should GM be assigned primary and CA secondary.

CA should receive a primary assignment when the research is concerned with the induction, promotion, progression and prevention of carcinogenesis initiated by biological, chemical or physical agents. All studies on the molecular or genetic mechanisms of anticarcinogenesis/carcinogenesis/oncogenesis/transformation in higher vertebrate systems should be given CA primary assignment. GM should be given primary assignment when the study deals with chemical and physical interactions of macromolecules with chemical agents, DNA replication and repair, mutagenesis, or drug metabolism, and when the study has a general biological focus. CA and GM should be given dual assignment, with CA secondary, for the above types of studies when there are minor components in which carcinogens are used or when mechanisms of anticarcinogenesis/carcinogenesis are a minor part of the study. Basic studies in model systems, such as lower vertebrates, invertebrates, and plants, should be given a GM primary assignment.

Studies on biological agents, transforming DNA, virus integration or oncogenic virus gene regulation, when they relate to carcinogenesis/anticarcinogenesis should be given primary CA assignments.

Studies of new drugs or natural products should be given CA assignments when the rationale for these studies is the development and evaluation of anticancer potential, including anticarcinogenic/chemopreventive potential. Synthesis of compounds primarily for the development of new methodology should be assigned to GM. Systems for delivering drugs or chemoprevention agents in the context of potential for cancer therapy or in the context of human intervention trials of cancer chemopreventive agents should receive CA primary assignments. Basic studies on anticarcinogenic/anticancer drugs, agents and/or natural products should be CA primary. Broader studies of drugs and drug delivery systems should be given GM primaries and CA secondaries where considered appropriate.

HD - CA should receive primary assignment when studies emphasize transplacental and fetal carcinogenesis/anticarcinogenesis, cancers of the young, and exposure to carcinogenic/anticarcinogenic agents early in life or populations early in their life span to investigate cancer etiology, prevention, or epidemiology. Common areas of interest would

include smoking and health, diet and nutrition, alcohol and drug abuse, and AIDS and HIV-associated malignancies in perinatally infected infants and children. CA should be given primary assignment for studies of the treatment of pain arising from cancer or its treatment in children and adolescents.

CA should be given primary assignment for studies that propose large-scale interventions, including clinical trials aimed at smoking prevention or cessation in adolescents or at promoting cancer specific risk-reduction behavior in adolescents. HD should receive primary assignment of studies aimed at adolescents to: determine how smoking of cigarettes is initiated; determine the process by which smoking becomes habitual behavior; research on smoking as risk-taking behavior; and research on risk-taking behavior and life-style modification for the aggregate of public health problems, including, but not limited to, cancer, which lead to premature morbidity and mortality. When the focus is on reducing the risk of cancer in women in general, CA should receive primary assignment, with HD as a possible secondary assignee. When the emphasis is on reducing the risk to the fetus by helping a pregnant woman reduce or eliminate smoking, the application should be assigned to HD primary and CA secondary.

Projects using teratocarcinoma or teratoma cells to study differentiation and neoplasia should be given CA primary assignment. If these cells are used as a model system for normal embryonic development, the study should be given an HD primary and a CA secondary assignment. The integration and function of genes into blastocysts, transgenic embryos and mice, and chimeric mice with the intent of studying cancer prevention, development and progression should be given CA primary assignment.

CA should be given primary assignment when the relationship of a reproductive factor to cancer risk is being evaluated. Epidemiologic studies to elucidate the relationship of hormones, including exogenous hormones such as oral contraceptives and menopausal supplements, should be given dual CA/HD assignment. Trophoblastic disease studies, including choriocarcinoma, should be given dual CA/HD assignment.

AGREEMENT ON REFERRAL GUIDELINES IN THE AREA OF MEDICAL REHABILITATION IS PENDING DISCUSSIONS BETWEEN CA AND HD.

HG - Studies designed to map specific anti-cancer and cancer-related genes to elucidate their roles in cancer prevention, oncogenesis, cancer diagnosis and/or prognosis should be assigned to CA. Studies evaluating interventions in groups identified as having genetically determined high risk should be assigned to CA. These include prevention and counseling. Assignment should be to HG when the emphasis is on mapping or DNA sequence determination of entire genomes or chromosomal segments.

HL - CA should receive primary assignment of all etiology, biology, prevention, diagnosis, treatment and epidemiology studies of cancers of the bronchopulmonary and hematopoietic systems, e.g., lymphoma or leukemia. This includes mechanistic and structural studies involving all subcellular components and factors produced by these cancer cells, as well as studies involving stem cell and bone marrow transplantation, gene marking, and gene therapy in cancer models and cancer patients.

CA should receive primary assignment for developmental studies of diagnostic imaging techniques (MRI, SPECT, ultrasound, imaging agents, etc.). When these techniques are applied to visualization of non-cancerous cardiovascular and pulmonary structures, HL should be primary and CA secondary.

When etiologic and epidemiologic aspects of bronchopulmonary and hematopoietic cancers are the focus of studies involving smoking and health issues, diet and nutrition, AIDS and HIV-associated malignancies in hemophiliacs, etc., CA should receive primary assignment. For studies where the primary disease interest is not clear or both CA and HL disease missions are prominently represented , such as in smoking and dietary investigations, dual assignments to CA and HL are appropriate, the primary assignee being CA or HL depending upon the judgement of referral officer. When emphasis is on the prevention or treatment of cancer, either preclinical (e.g., use of tumor cell lines) or clinical, in bronchopulmonary and hematopoietic systems, or on the effects of chemoprevention or cancer treatment on these systems, CA should be the primary assignee. CA should also be the primary assignee when research is designed to study the mechanisms of cancer prevention or treatment toxicity on heart, lung and vascular systems, e.g., factors responsible for raising and reducing toxicity or the design of chemical analogs with reduced toxicity.

BOTH CA AND HL HAVE INTERESTS IN APPLICATIONS CONCERNING SMOKING PREVENTION AND CESSATION.

HS - AGREEMENT ON REFERRAL GUIDELINES IS PENDING DISCUSSIONS BETWEEN CA AND HS.

LM - For studies involving radiographic image databases, where the major interest is diagnostic or treatment utilization of the image, its multidimensional visualization, or imaging tools, assignment should be to CA. Where the interest is in database organization, indexing, and retrieval, or the integration of image databases with other medical databases, assignment should be to LM.

MH - CA should have the primary assignment when the major thrust of the proposed research is testing interventions that address psychosocial variables that are a result of, or influenced by, cancer and its treatment.

When the major emphasis of a proposal is the psychosocial impact of pain related to cancer, the primary assignment should be to CA with MH as secondary.

NR - BOTH NR AND CA HAVE INTERESTS IN APPLICATIONS IN THESE AREAS. Studies that focus on the nursing care of cancer patients should be assigned to NR. Areas of overlap include symptom management (such as pain, nausea, fatigue), psychosocial support, patient education, health promotion and risk reduction, and nurse-delivered screening programs. CA should receive primary assignment when the research proposal is related to cancer care with a minor nursing component.

When the major emphasis is on a health promotion intervention study aimed at modifying personal or institutional behavior related to cancer risk reduction or cancer prevention and control, the primary assignment should be CA.

NS - BOTH CA AND NS HAVE INTERESTS IN APPLICATIONS IN THESE AREAS. CA should receive primary assignment for all studies of primary and secondary (metastatic) tumors of the central and peripheral nervous systems, when the emphasis is on understanding the pathology, etiology, prevention, treatment, cellular and molecular biology, biochemistry, immunology, diagnosis, and genetics of these cancers and the cancer process in general. This includes tumors of the cranial nerves, supporting structures, such as glia and meninges, and HIV-associated tumors. Neuroblastoma, glioma, and astrocytoma cell lines are models for studying tumor mechanisms and for differentiation therapy, and generally should receive CA primary assignments. When tumor cells are clearly used as model systems for understanding normal neural function, such as neurotransmission, NS should receive primary assignment and CA secondary assignment.

CA should receive primary assignment when the emphasis is on treatment of primary or metastatic central nervous system tumors, e.g., brain. This includes development of chemopreventive and/or antitumor drugs designed to cross the blood-brain barrier, interstitial radiotherapy, and use of novel radiation particles/radiation sensitizers. Studies on the effects of tumor on normal CNS function should be assigned to NS as primary.

CA should be given primary assignment if the studies involve viral oncogenesis. When neuropathologic diseases are caused by neurotropic tumor viruses such as the human papova viruses (e.g., JC virus) and wild mouse retrovirus, primary assignment should be given to NS.

CA should receive primary assignment when the emphasis is on treatment of pain arising from nervous system involvement due to cancer or its treatment.

OH - BOTH CA AND OH HAVE INTERESTS IN APPLICATIONS IN THESE AREAS.

CA should receive the primary assignment on studies of cancer that emphasize: the assessment of occupational exposures or carcinogens as risk factors or modifiers of known risk factors in human populations; evaluation of multiple risk factors, of which occupation is only one; a major thrust of research in cancer etiology or cancer epidemiology utilizing worker cohorts as high-risk populations exposed to occupational hazards; mechanistic research that will further our understanding of processes of carcinogenesis and/or tumor biology; and the development, validation, and application of laboratory measurement and biological markers that may elucidate the pathogenesis and origin of cancer related to occupational exposures.

OH should be given the primary assignment when: the study is focused on the control of hazards at the worksite; the study is focused on technology or equipment that enhances hazard control at the worksite, including personal protective technologies; the study is directed at determining criteria for occupational health standards; the study is focused on development of new analytical methods for field samples; and the study assesses an occupational environment to evaluate the biological effects of specific agents and their toxicities as they relate to health. Dual assignments to CA should be considered for OH primary assignments involving a cancer control intervention.

RR - BOTH CA AND RR HAVE INTERESTS IN APPLICATIONS ON AIDS AND AIDS-RELATED ANIMAL MODELS.

AWARD MECHANISMS

C06 Research Facilities Contruction Grant

F31 Pre-doctoral Individual National Research Service Award

F32 Post-doctoral Individual National Research Service Award

F33 National Research Service Award for Senior Fellows

F34 MARC NRSA Faculty Fellowship

F35 Intramural NRSA Individual Post-doctoral Program Appointee

F36 Mentored MARC Visiting Scientist Fellowship

K01 Research Scientist Development Award

K07 Academic/Career Award (Preventive Oncology)

K08 Mentored Clinical Scientist Development Award

K12 Mentored Clinical Scientist Development Award Program (by announcement only)

K22 Career Transition Award (NCI Scholars Program)

P01 Research Program Project

P20 Exploratory Grant

P30 Center Core Grant

P50 Specialized Center

R01 Research Project (Traditional)

R03 Small Grant

R13 Conference

R15 Academic Research Enhancement Award (AREA)

R18 Research Demonstration and Dissemination Project

R21 Exploratory/Developmental Grant

R25 Education Project

R24 Resource-Related Project

R29 First Independent Research Support and Transition (FIRST) Award

R37 Method to Extend Research in Time (Merit) Award

R41 Small Business Technology Transfer Grant (STTR)--Phase I

AWARD MECHANISMS CONT.

R42 Small Business Technology Transfer Grant (STTR)--Phase II

R43 Small Business Innovation Research Grant (SBIR) - Phase I

R44 Small Business Innovation Research Grant (SBIR) - Phase II

R55 Shannon Award

S03 Minority High School Student Research Apprentice Program

S06 Minority Biomedical Research Support - MBRS

S15 Small Instrumentation Grant

T32 Institutional National Research Service Award

T34 MARC Undergraduate NRSA Institutional Grant

T36 MARC Ancillary Training Activities (Grant)

U01 Research Project (Cooperative Agreement)

U10 Cooperative Clinical Research (Cooperative Agreement)

U13 Conference (Cooperative Agreement)

U19 Rearch Program (Cooperative Agreements)

U43 Small Business Innovation Research Grant (Cooperative Agreement) - Phase I

U44 Small Business Innovation Research Grant (Cooperative Agreement) - Phase II